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In Hong Kong, lung cancer is the commonest lethal malignant disease in both males and females. This thesis represented the first major clinical study of lung cancer (1979-1984) in the local Chinese population.

The patients were those admitted to the University Department of Medicine, Queen Mary Hospital, Hong Kong, and all had histologically or cytologically proven lung cancer. Histological typing was based on the World Health Organization Classification (1981), with 4 major types of lung cancer, namely (1) squamous cell carcinoma (SQ), (2) small cell carcinoma (SM), (3) adenocarcinoma (AD), and (4) large cell carcinoma (LA).

A prerequisite for a clinical study of lung cancer is accurate cell typing. My phase-one study was to assess collaborately with the Department of Pathology the cell typing accuracy of cytodiagnosis (bronchoscopic and sputum) in our hospital. In a five-year study period (1979-1983) in 573 patients, for both bronchoscopic and sputum cytologic cell typing, accuracy was highest in SQ and SM (76-100%), followed by AD (80-88%). That of LA was much lower (< 67%), but the number of patients was small.

The next phase is collection of clinical data base by a clinical review of 493 patients admitted from 1976 to 1980. The male to female sex ratio was low (1.87:1), reflecting the

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high incidence of lung cancer in women in Hong Kong. In men, SQ was the predominant cell type (44%), followed by AD (23%), SM (13%) and LA (7%), but in women, the preponderance of AD (44%; SQ 31%; SM 10%; LA 2%) is noteworthy. Cigarette smoking was a major factor in SQ and SM. The relative risk of lung cancer in smokers was 6.4 to 10.7 for SQ and SM, but was not significant with AD or LA (< 1.8). SQ and SM, being smoking-related, showed features of a centrally located tumour. Our AD, contrary to classical teaching, also showed clinical, radiological and bronchoscopic features of a centrally situated tumour.

A three-part study was then carried out in parallel from 1981 to 1984 :

(1) Clinical data were collected from 503 patients upon diagnosis from January 1981 to April 1984. The findings of the review study were confirmed. The male to female ratio was low (1.96:1). A history of cigarette smoking was strongly associated with SQ and SM. The relative risk of lung cancer in smokers was 5.8 with SQ and 21 with SM in men, and 10.5 with SQ and 33.9 with SM in women, but not excessive with AD and LA (1 to 2.1). In women, AD was the predominant cell type (56%), and 46% of all cases and 63% of AD were life-long non-smokers. Again, AD showed features of a predominantly centrally situated tumour.

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(2) That our AD, usually in non-smoker females and centrally situated, was intriguing. A case-control study of 163 female patients and 185 female controls was carried out to compare their exposure to three common environmental, inhaled substances, namely passive smoking, kerosene stove fumes and home incense burning. Analysis for non-smokers showed that kerosene stove and incense burning were not contributory factors ($p > 0.05$). Passive smoking was also not shown to be associated with AD of the central type, but may contribute to AD of the peripheral type ($p < 0.05$).

(3) The median survival of our patients with untreated, inoperable disease was poor, being 1 month for small cell cancer and 3.5 months for non-small cell cancers. We studied the effect of three combination chemotherapy schemes on survival of these patients. In 43 patients of small cell carcinoma, MACC (methotrexate, adriamycin, cyclophosphamide and CCNU) chemotherapy was effective (21% complete and 53% partial response), and significantly improved overall patients survival (median survival 50 weeks). In non-small cell cancers, however, MACC chemotherapy (in 42 patients) and FuAM/FiAM schemes (Futraful/5-Fluorouracil, adriamycin, mitomycin-C, in 44 patients of adenocarcinoma), were ineffective. Although partial response occurred in 5-27% of patients, there was no overall survival benefit.

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With a more solid data base, collaborative studies are now being initiated, including city-wide epidemiological studies, clinico-pathologic studies, and studies of host determinants.

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families, and should therefore be re-examined.

C. Incense Burning at Home - Burning of Chinese incense at temples in worship of idols or gods, a common scene in tourists books, is part of the traditional Chinese customs still practised in Hong Kong. Burning of incense at home, either for ancestor worship (traditional Chinese filial piety) or deity worship, is also common among the large non-Christian local population. Chinese incense smoke has been shown to contain carcinogens, (Schoental & Gibbard, 1967) but to-date, no studies have been undertaken to examine its relation to lung cancer. Given that (1) in Hong Kong, home incense burning is common, (2) that many adult women in Hong Kong are housewives who spend most of their time at home, inhaling incense smoke which contains carcinogens, & (3) that Hong Kong is overcrowded with many families living in houses/flats of area 400 to 800 square feet only, which would increase the inhaled dose of any potential "inhaled carcinogen" present in a small home area, it is conceivable that incense smoke might well be important in the genesis of lung cancer in our women who do not smoke.

A study was therefore carried out to examine whether passive smoking, kerosene stove cooking and incense burning at home are likely causative factors in lung cancer in non-smoking Chinese women. This forms Part C of the 1981-1984 lung cancer

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study, (see Chapter 5, pp 69).

7.2 Patients & Methods

This is a case-control study. The cases were all of the Chinese female patients who were admitted to the University Department of Medicine, Queen Mary Hospital, Hong Kong, between January 1981 and April 1984, with histologically and/or cytologically confirmed carcinoma of the lung of the four major cell types (Types 1-4, W.H.O. Classification, 1981). Great care was taken to exclude secondary carcinoma of the lung (see pp 18-19) but otherwise all Chinese female patients were included with no other selection criteria. Comparison patients (controls) were Chinese female patients admitted to the Orthopaedic wards in Queen Mary Hospital during the period 1982-1984, comparable to lung cancer patients in age and social class - both cases and controls were patients of the third class general wards and were mostly from the lower income group. Patients with pathological fractures due to smoking-related malignancies, and peripheral vascular disease-related orthopaedic conditions were excluded. It is considered that our orthopaedic controls should not be biased towards smoking-associated diseases.

All cases were interviewed by myself, and the controls by myself or Miss Cindy Ling, our technician and research assistant, who was trained for this investigation and thoroughly

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familiar with local culture. The questions covered dialect group, occupation, smoking habits, passive smoking, domestic cooking including kerosene stove, and home incense burning, in form of a standardized questionnaire (Fig. 7.1). For very ill patients, or for patients who spoke a dialect other than Cantonese or Mandarin, arrangement would then be made for their next-of-kin to be interviewed with the patients as interpreter.

Attempts at quantitation of passive smoking has been recognised as difficult (Royal College of Physicians, 1983; Weiss et al, 1983). Sidestream smoke, to which the passive smoker is exposed, is diluted by room air to a variable extent. The room air itself also contains smoke which has been inhaled and then exhaled into the air. Amount and duration of smoke exposure, the smokers' smoking habit, size and ventilation of rooms etc. are all important variables, and the amount of the various components of tobacco smoke breathed by the non-smoker from a smoky atmosphere are therefore extremely variable and unpredictable, and there are no agreed standards for expressing the extent of pollution of indoor atmospheres by tobacco smoke. The same problem applies to quantitation of exposure to kerosene stove cooking fumes and burning of incense at home. I had the opportunity of discussing this with Sir Richard Doll during his visit to the University Department of Medicine, Hong Kong, in

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FIG. 7.1. LUNG CANCER QUESTIONNAIRE

Name: _____ Sex/Age: _____ Date _____

Address (District): _____ How Long? _____ Dx: _____

Born in ☐ Hong Kong ☐ China In Hong Kong for ____yrs. Dialect Gp. _____

Occupation: _____ for _____ yrs. Schooling ☐ ≤ 6 yr. ☐ > 6 yr.

Marital Status: ☐ Single ☐ Married ☐ Widowed _____ yrs.

Husband: occupation _____

SMOKING: ☐ non-smoker ☐ ex-smoker _____ yrs. ☐ smoker

☐ cigarettes ☐ hand-rolled ☐ water-pipe ____/day x ____ yrs.

PASSIVE SMOKING:

Home: Size of home: _____ No. family members: _____

	Husband	Others		Father	Mother
Non-smoker	☐	☐	☐	☐	☐
Smoker: Amount	_____/day	_____/day	____/day	_____/day	___/day
Exposure/d	_____ hr.	_____/hr.	____/hr.	_____/hr.	___/hr.
Duration	_____ yr.	_____/yr.	_____/yr.	_____/yr.	___/yr.

AT WORK: Size of working place _____ No. of smoker workmates _____

Exposure time/day _____ hr. for _____ yrs.

DOMESTIC COOKING: ☐ Never/seldom cooks

☐ Cooks regularly

☐ Kerosene _____ yrs. ☐ Electricity _____ yrs.

☐ Coal gas _____ yrs. ☐ Gas _____ yrs. ☐ wood ____ yrs.

Chinese pan cooking ☐ yes ☐ no ____ times/wk for ____ yrs.

HOME INCENSE BURNING: ☐ Yes ☐ No for _____ yrs.

☐ Daily ☐ Festivals only

☐ Inside house ☐ Outside house

HISTORY OF PULMONARY TB: ☐ Yes ☐ No

Chest x-ray: (No.)

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November 1983, and he advised that it would be best to categorize exposure as positive and negative only with no further attempts at quantitation.

The significance level for the risk ratios are calculated for 2 tests, Test A and Test B. Test A is whether the risk-ratio is really greater than one, using the Bayesian risk ratio analysis method by Altchison and Bacon-Shone (1981). Test B uses a logistic regression model (Breslow & Day, 1980):

$$\log \frac{P\ (\text{cancer/risk})}{P\ (\text{no cancer/risk})} = \alpha + \beta \times \text{exposure}$$ (P : Probability)

The test is of whether $\beta > 0$, i.e. that the chance of cancer increases with exposure.

7.3 Results

A total of 163 cases and 185 controls were interviewed. Two cases (both were chronic smokers with small cell carcinoma) were too ill to be interviewed, and we failed to arrange meeting their relatives, and they were excluded from the study. Of the 185 controls, 80 were treated for fractures, 17 for infective bone and joint diseases (including tuberculosis), 15 for osteoarthrosis, 8 for rheumatoid arthritis, and 65 for other orthopaedic conditions.

Demographic characteristics of the cases and controls are compared in Table 7.1. The groups are similar in age, as

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indicated by the distribution in Table 7.1, and medians of 67.5 years for cases and 66 years for controls. Socioeconomic status (as measured by occupation, years of schooling) and recent residence are also similar in both groups. It is therefore considered not necessary to stratify these variables in the analysis.

The cases and controls' smoking habit was obtained in detail as described on pp 86-87, Chapter 5, and the results were presented in Table 5.8, pp 89, which is reproduced here as Table 7.2 for easy reference. The results were discussed in Chapter 5.

There were a total of 75 non-smokers in the cases and 144 non-smokers in the controls, and they form the study population for the present analysis.

No attempts at quantitation (except for Test B) was made as described above in Methods. When passive smoking (P), kerosene (K) and incense (I) were considered together, three intersecting circles can be drawn showing seven possible combinations of exposure, and one isolated circle (N) indicating those who had never been exposed to any of these sources (Fig. 7.2). Passive smoking includes exposure to smoking husbands, cohabiting relatives, or workmates.

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TABLE 7.1.

DEMOGRAPHIC CHARACTERISTICS OF THE CASES & CONTROLS

	Cases		Controls	
	No.	(%)	No.	(%)
Number	161		185	
Age (median, years)	(67.5)		(66)	
≤ 49 years	18	(11)	19	(10)
50-69 years	74	(46)	98	(53)
≥ 70 years	69	(43)	68	(37)
Places of origin from the southern province of Guangdong *	147	(91)	155	(84)
Never married	16	(10)	14	(8)
Occupation				
Housewife	95	(59)	134	(72)
Domestic servant	32	(20)	22	(12)
Labour/factory/hawker	31	(19)	25	(14)
Office/nurse/teacher	3	(2)	4	(2)
Schooling of ≥ 6 years	26	(16)	20	(11)
Recent residence				
Urban	150	(93)	177	(96)
Semi-urban/rural **	7	(4)	5	(3)
Boat (Fisherman)	4	(2)	3	(2)

* please see Fig 2.1, pp

** the New Territories (excluding the new satellite towns), and outlying islands.

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TABLE 7.2. CELL TYPE OF LUNG CANCER AND SMOKING HABIT IN 163 FEMALE PATIENTS WITH TYPES I-IV LUNG CANCER, 1981-1984

Type	I		II		III		IV		Controls
	No. (%)	RR	No. (%)	RR	No. (%)	RR	No. (%)	RR	No. (%)
Non-smoker	7 (25)	1	3 (9)	1	60 (62)	1	5 (71)	1	144 (78)
< 19 pack-yr	5 (18)		3 (9)		9 (9)		0 (-)		19 (10)
20-39 pack-yr	8 (29)		15 (47)		19 (20)		1 (14)		14 (8)
> 40 pack-yr	8 (29)		11 (34)		8 (8)		1 (14)		8 (4)
All smoker	21 (75)	10.5	29 (91)	33.9	136 (38)	2.1	2 (29)	1.4	41 (22)
TOTAL	28		32		96		7		185

I : Squamous cell; II : Small cell; II : Adenocarcinoma; IV : Large cell

RR : Relative risk, calculated as $\frac{\text{No. of smokers in cancer group}}{\text{No. of non-smokers in cancer group}} \times \frac{\text{No. of non-smokers in controls}}{\text{No. of smokers in controls}}$

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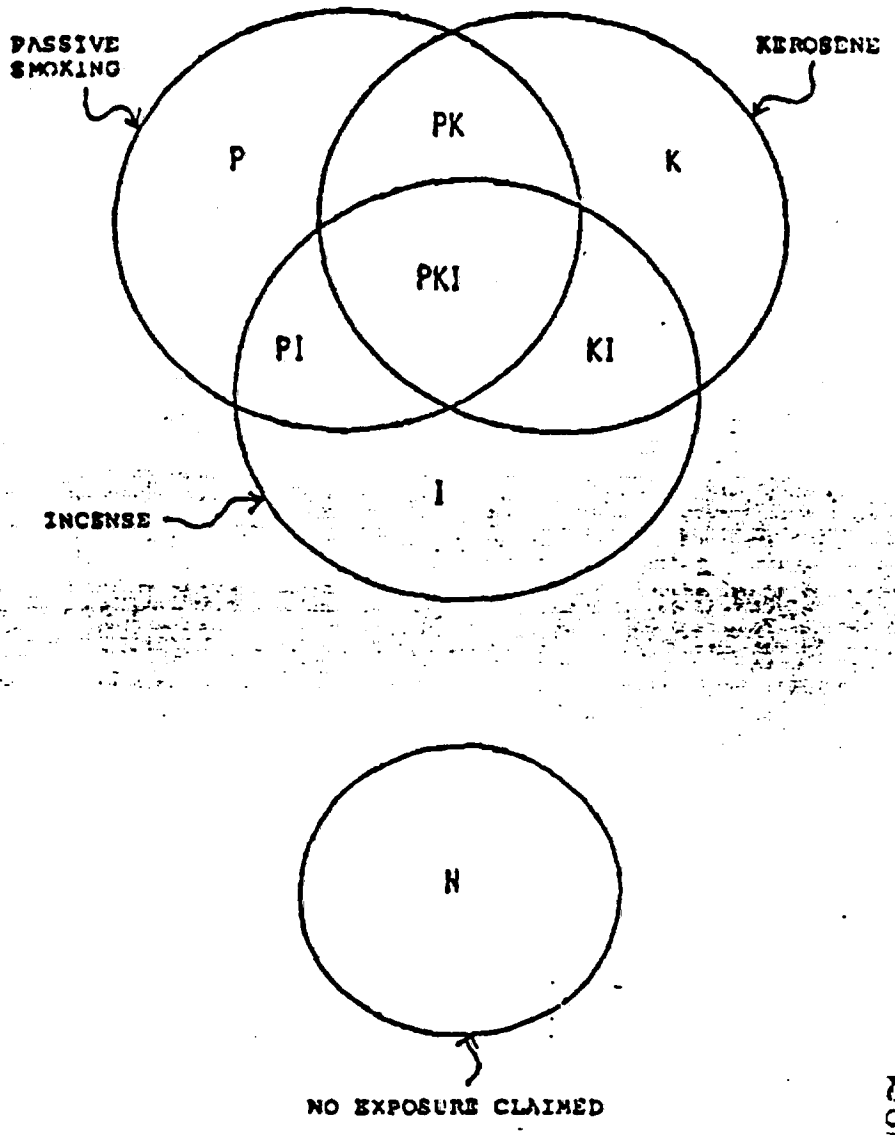
FIG. 7.2.

EXPOSURE CATEGORIES TO PASSIVE SMOKING, KEROSENE AND INCENSE



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The number of non-smoking cases with types 1 (squamous cell), 2 (small cell) and 4 (large cell) lung cancer are small -- being seven, three and five respectively (Table 7.3), and did not therefore afford meaningful statistical analysis. For type 3 adenocarcinoma, the pathogenesis of which we are most interested in, there were 60 non-smokers, and the proportions of different exposure categories are tabulated in Table 7.4. The cases are stratified into central and peripheral tumours to examine the contention that our preponderance of central adenocarcinoma might be related to inhaled carcinogens. The risk ratios (and their significance level) for exposure to passive smoking, kerosene and incense in our non-smoker adenocarcinoma female patients are shown in Table 7.5. Total passive smoking and passive smoking due to smoking husband alone are examined separately.

7.4. Discussion

The problem posed before us is the preponderance of adenocarcinoma of lung, usually in non-smokers, predominantly centrally situated, in our female population. This case-control study was carried out to compared exposure of cases and controls to three environmental, inhaled substances, namely passive smoking, kerosene stove cooking fumes and home incense burning fumes. The results showed that (Table 7.5) kerosene and incense

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TABLE 7.3.

DIFFERENT EXPOSURE CATEGORIES FOR TYPES 1, 2 & 4 LUNG CANCER IN NON-SMOKING WOMEN

Exposure* Category	No. of cases			No. of controls
	squamous cell (1)	small cell (2)	large cell (4)	
P	-	-	1	3
K	-	-	-	6
I	-	-	-	13
PK	3	1	-	21
PI	-	-	1	17
KI	-	-	-	35
PKI	4	2	3	40
N	-	-	-	9
Total	7	3	5	144

* please refer to Fig.7.2.

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TABLE 7.4.

DIFFERENT EXPOSURE CATEGORIES FOR ADENOCARCINOMA OF LUNG IN NON-SMOKING WOMEN

Exposure * Category	No. of cases		No. of controls
	Central	Periphoral	
P	1	-	3
K	3	1	6
I	-	1	13
PK	7	7	21
PI	5	6	17
KI	6	5	35
PKI	9	8	40
N	1	-	9
Total	32	28	144

* please refer to Fig.7.2.

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are not contributory factors for adenocarcinoma, central or peripheral. Although the risk ratio of passive smoking is greater than one for central adenocarcinoma, the level of significance is only about 10 per cent by Test A. There is however suggestion of passive smoking associated with peripheral adenocarcinoma, particularly passive smoking due to smoking husbands. The differences between Tests A and B in Table 7.5 could be due to a non-linear logistic dose-response curve or to errors in assessing the level of exposure due to incomplete information.

There has been only one published report of passive smoking in female lung cancer patients in Hong Kong (Koo et al, 1983). Koo found that passive smokers as a group had a relative risk of less than one. 40 of the 56 non-smoker patients (71.4%) and 83 of the 85 non-smoker controls (74.1%) have been exposed to passive smoking, which is not statistically different. The patients however included all cell types and were heterogeneous in this sense. In addition, the author did not distinguish central and peripheral tumours.

The association of passive smoking and lung cancer should be further pursued. There is good theoretical support for the association. Recently, it was reported that, like active smokers, the passive smoker is exposed to the same

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radioelements in the tobacco, as 50 to 70 per cent of the ^{210}Po appears in sidestream smoke (Winters & DiFrenza, 1983). In addition, the exposure of the passive smoker to naturally occurring radon daughters is increased in a smoky environment. It was estimated that radon daughter exposure could account for 20 to 100 per cent of lung cancers seen in non-smokers (Harley & Pasternack, 1981; Winters & DiFrenza, 1983). The conflicting findings of the Japanese (Hirayama, 1981) and American (Garfinkle, 1981) studies might be due to differences in methodology (Weizz et al, 1983). A potentially important factor is that the American study lacked smoking data on 73% of the husbands of nonsmoking women in comparison to only 28% in the Japanese study, which may have created biases in the data. A greater number of working women, larger homes and a higher divorce rate in the United States are other factors that could serve to account for the differences in results between these studies. In Hong Kong, the problem of overcrowding is notorious, with many families living in houses/flats of area 400 to 800 square feet only, and this would increase the inhaled dose of any potential inhaled carcinogen present in home environment. Previous estimates would have estimated the attributable risk of lung cancer due to passive smoking to be 30% greater in non-smokers exposed regularly to passive smoke

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compared to nonsmokers not exposed (Leeds, 1978). It has been found that both the Japanese and the American studies were in fact consistent with such an effect (Weiss, 1983).

The apparent association between passive smoking and peripheral adenocarcinoma (and not central tumours) in our patients is unexpected, and the reason unclear. It is known however that there is a difference in chemical composition of mainstream and sidestream smoke (Stock, 1980; Correa et al, 1983; Weiss et al 1983). Mainstream smoke emerges into the environment after having been drawn through the cigarette, filtered by the smoker's own lungs, and then exhaled. Sidestream smoke arises from the burning end of the cigarette and enters directly into the environment. All these lead to marked differences in the concentration of the constituents of mainstream and sidestream smoke, and many potentially toxic gas phase constituents, including nitrosamine, are in higher concentration in sidestream smoke than in mainstream smoke, and nearly 85% of smoke in room results from sidestream smoke (Weiss et al, 1983). It is true, of course, that sidestream smoke is generally diluted in a considerably larger volume. Thus, passive smokers are exposed to a quantitatively smaller and qualitatively different smoke exposure than active smokers. Whether this might produce different proportion of histological

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types of tumour (preponderance of adenocarcinoma), with peripheral location remains, at present, conjectural.

Two of the limitations of the present study are the relatively small number of subjects studied, and the inclusion of only one hospital, albeit a large, regional general hospital. Large, city-wide multi-hospital studies are warranted, and we are currently overcoming the immense logistic problems and pursuing further collaborative studies in this area (vide infra).

7.5. Conclusion

1. Our results showed that kerosene stove fumes and home incense burning are not contributory factors for adenocarcinoma of lung, whether central or peripheral. Passive smoking is also not shown to be associated with adenocarcinoma of the central type. The reason for the preponderance of central adenocarcinoma in our non-smoker female patient population has therefore remained unanswered.

2. There is however suggestion of passive smoking associated with peripheral adenocarcinoma, particularly passive smoking due to smoking husbands. The reason for the peripheral location of the associated tumour is

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not clear, although it is known that passive smokers are exposed to a qualitatively different smoke as compared to active smokers.

3. These findings need to be confirmed by large, city-wide, multi-institutional studies.

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